INSULIN + NUTRITION CONTROL FOR TIGHT CRITICAL CARE GLYCAEMIC REGULATION

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Abstract: A new insulin and nutrition control method for tight glycaemic control in critical care is presented from concept to clinical trials to clinical practice change. The primary results show that the method can provide very tight glycaemic control in critical care for a very critically ill cohort. More specifically, the final clinical practice change protocol provided 2100 hours of control with average blood glucose of 5.8 +/- 0.9 mmol/L for an initial 10 patient pilot study. It also used less insulin, while providing the same or greater nutritional input, as compared to retrospective hospital control for a relatively very critically ill cohort with high insulin resistance.

Keywords: Biomedical Control, Control Algorithms, Non-Linear Models, Physiological Models, Physiology, Medical Systems.

1. INTRODUCTION

Hyperglycaemia is prevalent in critical care, and worsens outcomes, increasing the risk of severe infection, myocardial infarction, neuropathy, and multiple organ failure (Krinsley, 2003; Van den Berghe *et al.*, 2001). Tight glucose control can reduce mortality by up to 45%. However, insulin-mediated control, is severely challenged in critical care by very high effective insulin resistance (McCowen *et al.*, 2001; Mizock, 2001). Glycaemic reductions are thus limited by insulin effect saturation at high concentrations (Prigeon *et al.*, 1996). Next, high glucose content nutritional support exacerbates hyperglycaemia (Weissman, 1999) and studies with lower glucose nutrition alone saw large reductions in glucose levels (Patino *et al.*, 1999).

2. MODELS and METHODS

This research presents the development of an insulin nutrition method for tight glycaemic control in critical care. First, a virtual cohort is used to develop the method in simulation. Second, the methods are tested in limited proof of concept clinical trials. Finally, a paper-based method that mimics the computerised controller is introduced as a clinical practice change for long-term testing to validate the overall concept.

2.1 Control Model

Chase et al (2005a) used a system model that that included insulin utilisation, losses and saturation.

$$\dot{G} = -p_G G - S_I (G + G_E)\frac{Q}{1+\alpha_G Q} + P(t) \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{V} \quad (3)$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pd}(t-t_i)} \text{ where } \overline{P}_{i+1} < \overline{P}_i \quad (4)$$

$$P(t_i < t < t_{i+1}) = \overline{P}_{i+1} + (\overline{P}_i - \overline{P}_{i+1})e^{-k_{pu}(t-t_i)} \text{ where } \overline{P}_{i+1} > \overline{P}_i \quad (5)$$

where $G(t)$ [mmol/L] is the plasma glucose above an equilibrium level, G_E [mmol/L]. $I(t)$ [mmol/L] is plasma insulin concentration resulting from exogenous insulin input, $u_{ex}(t)$ [mU/min]. $Q(t)$ [mU/L] is interstitial insulin concentration and k [1/min] accounts for the effective life of insulin in the system. Patient endogenous glucose clearance and insulin sensitivity are p_G [1/min] and S_I

[L/(mU.min)], respectively. V [L] is the insulin distribution volume and n [1/min] is the constant first order decay rate for insulin from plasma. Total plasma glucose input is denoted $P(t)$ [mmol/(L.min)]. k_{pr} is the rise rate of rate of plasma glucose input from enterally administered feed [1/min]. k_{pd} is the decay rate of rate of glucose input into plasma from enterally administered feed [1/min]. $\overline{P}_i$, $\overline{P}_{i+1}$ are stepwise consecutive enteral glucose feed rates [mmol/L.min]. Michaelis-Menten functions model saturation, with α_I [L/mU] for the saturation of plasma insulin disappearance, and α_G [L/mU] for the saturation of insulin-dependent glucose clearance. In this research, k, n, α_G, α_I and V are identified from generic population values. Details of the model, its development, and control analyses presented for it and similar models models can be found in (Chase, *et al.*, 2005a).

2.2 Control Method

In this study, non-steady stepwise enteral glucose fluxes are employed for control and modelled using the 2-compartment model in Eqs. (4-5). The exponential rates for total glucose rate of appearance (GRa) rise (k_{pr}) and decay (k_{pd}) model the effect of transient net hepatic glucose output and glucose disposal. Impaired splanchnic and peripheral glucose uptake imply a slow decay rate in total GRa following nutritional feed reduction (Kiwanuka *et al.*, 2001). Conversely, the rate of peripheral appearance of oral glucose is approximately equal to the intestinal absorption rate, implying a rapid rise following a nutritional increase (Radziuk *et al.*, 1978). Thus, k_{pr} and k_{pd} are set to 0.0347min^{-1} and 0.0068min^{-1} (half-lives of 20 and 100mins) to reflect this data.

The controller targets 10-15% hourly glycaemic reduction to 5mmol/L using a combination of insulin bolus, infusion and/or feed rate change. The goal is blood glucose in the 4-6mmol/L band. Thus, insulin sensitivity, S_I, is fitted from the prior hours' data before each intervention (Hann *et al.*, 2005) and endogenous clearance, p_G, is set to 0.01min^{-1}, a value found to be insensitive across this type of cohort (Hann *et al.*, 2005). Finally, the required combination of insulin bolus, insulin infusion rate and/or nutritional feed rate to achieve the hourly target glucose is determined iteratively using the updated S_I, value and Eqs. (1)-(5).

2.3 Virtual Cohort and Simulated Trials

The patient cohort includes 17 patients from a 201 patient data audit plus 2 patients from a hyperglycaemia control clinical trial (Chase *et al.*, 2005b). It represents a general cross-section of ICU population, in medical subgroup, APACHE II score, age, sex and mortality. Each record has glucose measurements every 3h or less. The average length is 3.9 days (range: 1.4-18.8). The cohort details are in Table 1. Ethical consent was granted by the Canterbury Ethics Committee.

Virtual trials use the retrospective fitted patient profiles of S_I and p_G, to simulate physiological patient response. It assumes these parameters are independent of the control inputs administered, creating a virtual patient response for any glucose or insulin inputs. Normally distributed error of ±7% is added to measured glucose values to include typical glucometer measurement error.

Table 1: Long-Term Virtual Trial Patient Cohort

Patient number	Medical subgroup	Apache II score	Age	Sex	Mortality	Diabetes
1	Sepsis	17	56	M		Type 2
2	Sepsis	24	64	M		
24	Other medical	25	47	M	Y	Type 1
87	Other medical	26	62	F		
130	Trauma	11	21	M		Type 1
229	Cardiac	15	73	F		
289	Cardiac	18	70	M		
468	General surgical	32	76	M		
484	Other medical	34	30	F		
486	General surgical	22	76	F		Type 2
519	General surgical	29	69	M		Type 2
554	Other medical	26	20	F		Type 1
666	Cardiac	8	44	F		Type 2
847	Other medical	17	67	F		
1016	General surgical	20	37	F		Type 2
1025	Pulmonary	36	48	M		Type 2
1090	General surgical	Unknown	37	F		
1099	Pulmonary	Unknown	24	M	Y	
1125	Other medical	Unknown	72	F	Y	

Each patient is tested using the control method. Results are compared to retrospective hospital data and an insulin-only control protocol (Chase *et al.*, 2005a). The control method uses three basic steps:

- Measure glucose every 30 minutes
- Every hour fit SI based on prior hours data
- Determine the insulin and nutritional changes to meet target reduction

Frequent measurement ensures tight control and safety. Hence, these trials are used for proof of concept testing of the insulin plus nutrition control concept. Less frequent measurement would be required for long-term clinical care.

2.4 Clinical Trials Method

The methods developed virtually are tested in short 10-hour proof-of-concept trials and one 24-hour trial. Inclusion criteria: *in situ* enteral feeding tube; random glucose level >8mmol/L; age >16 years; and an *in situ* cannula. Exclusion criteria: delayed gastric emptying; moribund; neuromuscular blockade; and morbid obesity (BMI>35kgm^{-2}).

Patients are fed enterally with RESOURCE™ Diabetic (Novartis Medical Nutrition, USA) up to 700kcal/day of glucose using a Ross Products Patrol Enteral Pump (Abbott Laboratories, Abbott Park, Illinois, U.S.A.). Actrapid™ insulin (Novo Nordisk, Bagsvaerd, Denmark) is infused with a 3500 syringe pump (Graseby Medical Limited, Colonial Way, Herts, UK). Ethical approval was obtained from the Canterbury Ethics Committee.

The overall trial protocol is shown in Figure 1. During the 2-hour pre-trial period, the insulin

infusion is kept constant to estimate the onboard insulin level in steady state. The blood glucose level at 0900h is taken as the equilibrium blood glucose, G_E. At 0900h, feed rate is decreased by 30-40% depending on current glucose level and feed rate as an initial challenge. Hourly glucose targets are set for a 10-15% reduction to a 5mmol/L minimum. Insulin sensitivity, S_I, is re-evaluated every hour using the prior hours' data. The controller prescribes insulin bolus size, insulin infusion rate, and feed rate to achieve the target.

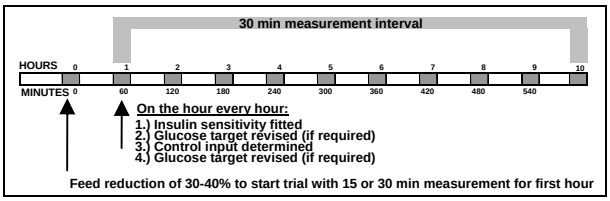

Fig.1: Clinical Trial Procedure

Note that glucose is only measured hourly for the 24-hour trial. This trial tests the ability of the controller to use less frequent measurements as a final step towards clinical, long-term testing.

Insulin is limited to 6U/hr to minimise saturation and saturated, ineffective insulin is limited to 30mU/L. The minimum feed rate is 280kcal/day of glucose or 40% of maximum for a total caloric intake of 778kcal/day (Novartis, 2005). This level exceeds the level found to avoid increased risk of bloodstream infections (Rubinson *et al.*, 2004).

2.5 Clinical Trials Cohort

The clinical trial patient cohort (n = 8) represents a heterogeneous cross-section in age and sex, as shown in Table 2. The median APACHE II score is 23 with inter-quartile range [19, 25]. The mean age is 64.8 ± 7.8 years.

Table 2: Clinical Trial Patient Cohort

Patient number	Medical subgroup	APACHE II score	APACHE II ROD (%)	APACHE III	SAPS II	SAPS II ROD (%)	Age	Sex	Mortality	Diabetes
1	Sepsis	17	14.3	40	15	2	56	M	N	Type 2
2	Sepsis	24	49.7	59	35	16.7	64	M	N	
3	Pulmonary	31	73.3	85	45	34.8	60	M	N	
4	Sepsis	26	59.7	91	62	71.9	75	F	N	
5	Sepsis	21	33.2	58	34	15.3	73	M	N	Type 2
6	Other medical	17	14.3	44	44	32.6	57	M	N	
7	General surgical	23	62.3	84	57	61.9	73	F	N	Type 2
8	Other medical	Not available					60	M	N	

2.6 Long-term Testing – The SPRINT Protocol

The clinical methods are developed and tested, first virtually and then in short proof of concept case studies. The final step is long-term clinical testing of this nutrition and insulin control approach. However, the measurement frequency must be reduced to 1-2 hourly for clinical ease of use. In addition, the methods must be removed from a computer and made paper based for easy uptake by clinical staff.

The SPRINT (Specialised Relative Insulin Nutrition Tables) protocol is designed to nearly exactly mimic the computerised trial protocol, as an easy-to-use equivalent. It consists of two wheels dedicated to enteral nutrition and insulin bolus administration, as shown in Figure 2. Instructions are printed on the wheels and hourly blood glucose measurements are used to determine the next hour's intervention.

The instructions on the "Feed Wheel" are used to determine the rate of feed as a percentage of the patient's clinically determined goal feed. The result is based on the previous hour's feed level, the current blood glucose concentration and whether blood glucose is rising or falling. The percentage goal feed is converted into an absolute feed rate (in ml/hr) using a patient-specific conversion sticker. The "Insulin Wheel" is then used to determine the insulin bolus size based on the previous insulin bolus size, the current blood glucose level and whether the blood glucose has decreased by more than 1.5mmol/L. The method is effectively fully automated once clinical staff take the hourly glucose measurement.

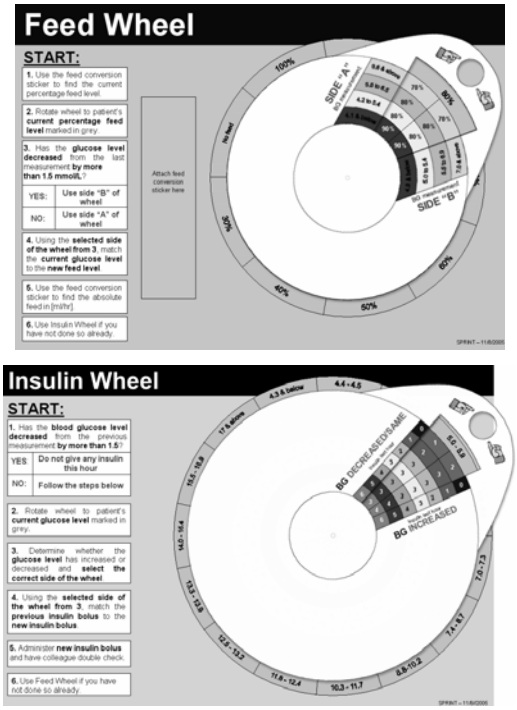

Fig.2: SPRINT feed and insulin wheels.

Hourly blood glucose measurements are used to ensure tight control. Two-hourly measurements are used when the patient is stable, defined as 3 consecutive measurements in the 4-6 mmol/L band. For two-hourly measurements, the feed rate is maintained and the same insulin bolus administered on the hour between measurements. Two-hourly measurements are continued until the patient leaves the 4-6 mmol/L band. SPRINT is stopped when the patient is stable, and normoglycaemic, defined as 6 or more hours in the 4-6.1mmol/L band, with over 80% of goal feed rate and a maximum of 2U per hour of insulin. Finally, insulin is always administered via bolus for patient safety, avoiding infusions being left on.

The specific wheel layout resulted from extensive consultation. ICU staff were proficient in minutes and reported the system as very easy to use. A nursing survey reported that 25 of 27 respondents viewed the wheels as satisfactory or better, with 13 rating it very good or higher. The covered wheel reduces table complexity, which reduces error.

3. RESULTS and DISCUSSION

3.1 Virtual Trial Results

Figure 3 shows Patient 87 from retrospective hospital data, the insulin-only protocol (Chase *et al.*, 2005a), and the variable feed and insulin protocol developed. Tight control in the 4-6mmol/L desired band is clear with the variable nutrition protocol compared to the other protocols. The total insulin administered by the variable nutrition protocol is 38.5% less than the insulin-only protocol (410.5U versus 667.0U). From the retrospective data, the total insulin infused was 248.0U, indicating another source of poor control. Time spent in the desired 4-6mol/L band was 89% versus 21.8% for the insulin-only protocol and 10.7% for hospital control. Finally, the results are achieved with total enteral glucose administered identical to the retrospective patient data (1284g versus 1286g).

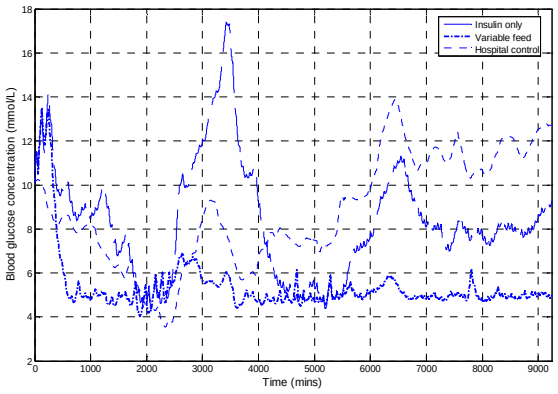

Fig.3: Patient 87 Virtual Trial Results

A summary of the results for all patients is shown in Table 3. The variable nutrition and insulin controller increased the time spent in the 4-6mmol/L band by 240% compared to the insulin-only protocol and 312% versus the retrospective data. Time above 6mmol/L is reduced by 231% and 237%. No hypoglycaemic events occurred for any virtual trial protocols. Figure 4 summarises these results plotting percentage time in the 4-6mmol/L band versus log mean fitted S_I.

Figure 4 shows that percentage time-in-band and mean blood glucose level decrease for all protocols with decreasing insulin sensitivity. With insulin alone, performance is highly dependent on the patients' effective insulin resistance (R=0.90, p<0.001) due to saturation limitations (Chase *et al.*, 2005a). The variable feed rate and insulin protocol provided tighter blood glucose control across the range of observed insulin sensitivities with significantly higher time-in-band (R=0.57, p<0.02). The insulin-only protocol only reached similar levels only at high insulin sensitivities, and with significantly more administered insulin. For hospital control, greater variation in blood glucose control was recorded, as expected (R=0.49, p<0.04), and showed tighter control than the insulin-only protocol only at low insulin sensitivities, where clinically selected feed reductions have affected the comparison.

Table 3: Blood Glucose Summary – Virtual Trials

		Mean Blood Glucose			Percentage of time in 4-6mmol/L band (%)		
Controller Type		Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale	Variable feed and insulin	Constant feed-rate, variable insulin	Hospital sliding-scale
Patient No.	1	6.0	12.1	9.3	66.8	1.6	10.2
	2	5.9	9.8	7.8	78.4	0.9	3.6
	24	6.6	12.4	12.2	80.1	0.0	0.0
	87	5.4	8.4	8.8	89.1	21.8	10.7
	130	7.0	13.2	11.2	60.1	0.0	10.3
	229	5.4	7.7	7.5	84.6	30.2	15.5
	289	5.3	5.5	6.8	80.8	79.8	13.2
	468	8.5	10.4	7.4	43.4	0.0	18.5
	484	7.5	12.3	11.5	70.0	0.0	0.0
	486	6.5	9.4	8.9	60.7	10.6	12.0
	519	5.6	7.8	6.3	78.6	51.4	33.9
	554	6.0	7.6	6.9	66.5	36.1	20.9
	666	7.2	12.4	5.3	35.7	0.0	74.9
	847	6.2	6.2	7.3	75.5	75.7	21.7
	1016	7.5	9.4	7.2	24.7	0.0	10.7
	1025	6.4	7.9	8.0	59.5	41.3	21.0
	1090	5.2	5.3	3.9	84.4	82.6	46.8
	1099	5.3	5.5	6.5	88.6	82.4	35.8
	1125	5.9	7.3	5.4	61.0	21.8	51.8
Mean		6.3	9.0	7.8	67.8	28.2	21.7
S. D.		0.9	2.6	2.2	17.9	31.8	19.3
Range		3.3	7.9	8.3	64.4	82.6	74.9

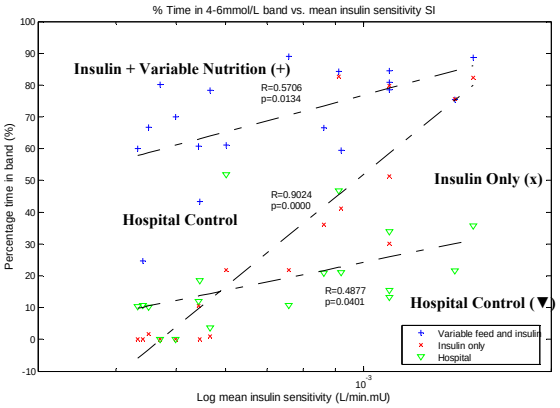

Fig.4: Mean Insulin Sensitivity, S_I, versus Time in the 4-6mmol/L Band

In summary, these results all indicate the effectiveness of using nutrition as an added control input. In particular, high APACHE II score, very critically ill patients are generally highly insulin resistant. Thus, this added control path may represent the only means to maintain euglycaemia, as well as one that is not saturable as is the insulin path.

3.2 Clinical Trial Results

The main goal of the clinical trials was to prove the insulin and nutrition control concept by illustrating the potential for tight control. Tight control is shown by accurately reducing glucose

levels to pre-set target values. Hence, the target error is the main performance criteria for evaluation.

The mean target error for all trials is 9.3% (0.52mmol/L), absolute range [0, 2.9] mmol/L, and 41.9% of targets are achieved within ±5% with a mean target error of 2.6% (0.15mmol/L). Mean target error for errors >5% is 14.3% (0.79mmol/L). Out of 86 targets, only seven had errors >20%, so that 90.7% of all measurements are within ±20% of targets. More specifically almost 90% of target errors are explainable by measurement errors (Weitgasser *et al.*, 1999). Outliers are attributed to significant and rapid changes in patient condition observed, such as atrial fibrillation. Model prediction errors at a 60min glucose measurement frequency (Trial 8) were not statistically discernible from the other trials.

Figure 5 presents a bootstrapped linear regression model applied to the achieved and target glucose values using 6000 bootstrap samples. Also shown are the non-parametric 95% confidence intervals (CI) for the prediction of achieved glucose values for a given target. A correlation coefficient between 0.7695 and 0.8983 can be stated with 95% confidence.

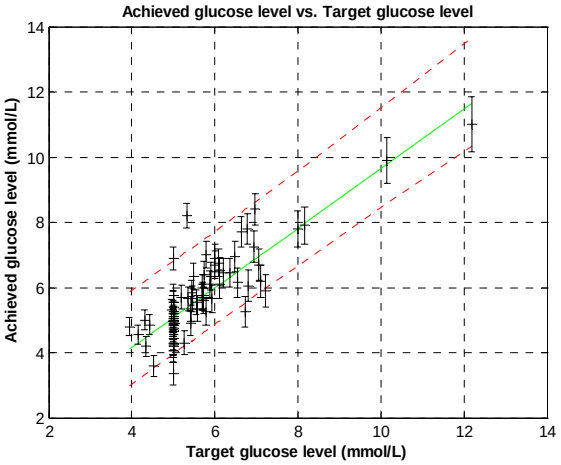

Fig.5: Target Error Summary

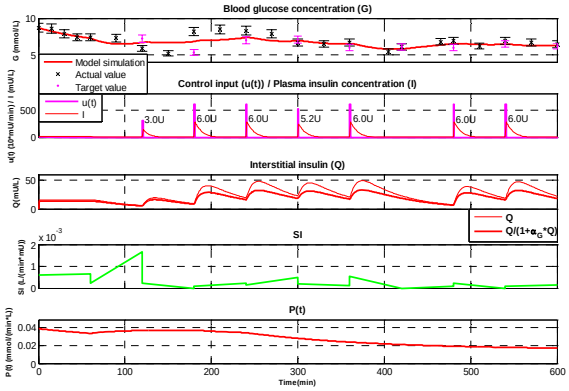

Fig.6: Patient 2 Clinical Trial Progression

Finally, Figure 6 shows a typical trial result for Patient 2. This trial highlights a common difficulty in critical care glycaemic control, the highly dynamic patient with rapidly evolving condition. The glucose measurement at 150mins was on course for the 5mmol/L target at 180mins. However, the recorded measurement at 180mins was 8.5mmol/L. The patient experienced atrial fibrillation at approximately 200mins, indicating that the change may have been due to adrenergic surge preceding the cardiac event. From that point, effective insulin resistance increased, requiring greater insulin input and feed rate reductions compared to the initial 60-120mins. The controller adapted to this not uncommon event, tracking the glucose measurements accurately within the next hour and the 300min target with 5.1% error.

3.3 SPRINT Results

The SPRINT protocol was implemented as a clinical practice change in the Christchurch Hospital ICU. The entry requirement was 2 successive random glucose measurements over 8 mmol/L. this limit ensures only the relatively more critically ill, and thus potentially more insulin resistant, patients are considered.

An initial pilot study of 10 patients was performed to test SPRINT over long term clinical care. The cohort had an average age of 54 (range: 44-80), average APACHE II score of 23 (range: 11-37) and an average APACHE III score of 70 (range: 34-108). There were 6 males and 4 females.

The total controlled time is 2103 hours with 1579 measurements indicating that 49.8% of the controlled time was on 2-hourly measurement as the patients were glycaemically stable. The average length of control for each patient was 210 hours (8.75 days), also indicating a significantly critically ill cohort.

The overall control results can be summarised:

- Average Blood Glucose = 5.8 +/- 0.9 mmol/L
- Average Insulin = 2.5 U/hour
- Average Feed Rate = 64% (1279 kcal/day)
- Time Feed Rate > 50% of goal feed = 70%

However, more relevant performance is time in glycaemic band and any hypoglycaemic events. The primary bands are the 4.-6.1 mmol/L band defined by van den Berghe et al and the 4-7.75 mmol/L band defined by Krinsley. More importantly, these bands are associated with reductions in mortality of 45% and 20-30% respectively, as well as significant reductions in other negative clinical outcomes. The overall glycaemic performance is thus summarised:

- Time in the 4-6.1 mmol/L band = 64%
- Time in the 4-7.0 mmol/L band = 89%
- Time in the 4-7.75 mmol/L band = 97%
- Number measurements < 4 mmol/L = 23 (1.5%)
- Number Measurements < 3 mmol/L = 0
- Minimum Blood Glucose = 3.2 mmol/L

Thus, the results indicate that SPRINT provided very tight glycaemic regulation. The values for time in the glycaemic bands from the landmark studies on hyperglycaemia and mortality are also very high. This latter result indicates that glycaemic levels were not only tightly controlled on average, but that their variation was also very limited. This result is backed up by the narrow 0.9 mmol/L standard deviation. Overall, the results indicate that modulating nutrition and insulin, in combination with frequent measurement, can provide very tight control for a very critically ill cohort.

4. CONCLUSIONS

This paper has presented the development, from concept to clinical practice change, of a nutrition plus insulin control methodology for maintaining euglycaemia in critical care. The methods are developed from a model-based virtual study to proof of concept clinical trials using a model based controller. The control method is then made paper based through a system that effectively mimics the model-based control methods, and implemented as a clinical practice change. Thus, the overall methodology of using retrospective data through to clinical change is also presented as an approach to developing this type of model-based control therapy.

The overall results indicate that modulating nutrition and insulin is an effective approach to controlling hyperglycaemia in critical care. In particular, the more critically ill cohorts with higher APACHE II scores are typically more insulin resistant and this path may offer the only approach to lowering glucose levels to within a desired level or band. Also apparent in the need for higher measurement frequency to ensure that dynamic patients are well monitored and that inappropriate interventions of nutrition or insulin are not maintained when patient condition evolves significantly.

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